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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: **METHOD FOR DELIPIDATION OF SKIN AND CERUMEN REMOVAL**

(57) Abstract

The invention relates to the field of skin and hair care products. Uncomplexed or loosely complexed cyclodextrin is the active ingredient of a composition which may be used to remove cerumen from the ear canal, or to cleanse the skin or hair.

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METHODS FOR DELIPIDATION OF SKIN AND CERUMEN REMOVALField of the Invention:

5 This invention is related to methods of removing lipids from the skin and hair and for removing cerumen from the ear canal.

Background of the Invention:

10 Sebaceous glands secrete sebum which contain lipids which collect on the skin and in the ear canal. The rate of secretion depends on several factors. Several skin disorders, including acne and seborrhea, are associated with inappropriate sebum production.

15 The removal of excess lipids from the skin can usually be accomplished by bathing using detergents and cleansers. Many preparations have been developed to assist in removal of excess lipids. U.S. patent 5,026,551 discloses compositions comprising carbon dioxide gas and emulsifiers with oils in bath preparations. In one embodiment the carbon dioxide gas was carried on cyclodextrin. U.S. patent 4,970,072 discloses use 20 of whey products in bath preparations.

25 Cyclodextrins have been used as delivery agents for water-insoluble drugs for topical, oral and parenteral delivery. They have also been used to deliver cosmetic preparations to the skin. Several compositions utilize cyclodextrin inclusion products. European patent application 0 366 154 (1990) discloses several cyclodextrin inclusion products for use in cosmetic compositions. U.S. patent 4,678,598 discloses and claims a cyclodextrin-containing shampoo containing menthol and camphor. The cyclodextrin is provided to depress odor. U.S. 30 patent 4,267,166 discloses use of cyclodextrin to treat foul breath. U.S. patent 4,891,361 discloses use of a kojic/cyclodextrin inclusion complexes to prevent elastosis in an animal test by preventing formation of melanin. A publication of Wacker Chemicals discloses that empty cyclodextrins in powder or creams may contain excreted matter of the skin or reaction substances produced on the skin. The statement by Wacker is under a subheading, "masking of disagreeable smells" 35 and contains four other statements, all of which pertain to

odorous substances. The sebaceous skin lipids are not odorous. Therefore, it appears that the Wacker publication was referring to the containment of unpleasant odors that are produced when bacteria act upon lipids and other skin secretions. There is no evidence therein the materials were useful as cleansing agents for delipidation of the skin.

Summary of the Invention:

The present invention provides delipidating compositions containing essentially oil-free "empty" cyclodextrin compositions. It also provides compositions for use in removal of cerumen from the ear. The compositions containing "empty" cyclodextrin advantageously avoid use of harsh, drying agents or injurious mechanical methods.

Detailed Description of the Invention:

Cyclodextrins are cyclic oligomers of glucose that are derived from starch, and that consist of rings of glucose molecules. The three most common forms, alpha-, beta-, and gamma-cyclodextrins consist, respectively, of six, seven and eight glucose molecules. The molecules contain cavities that have lipophilic properties. Cyclodextrins present an advantage as natural substances that are nontoxic and nonirritating to the skin. Empty cyclodextrins have often been sold for use in preparation of inclusion complexes. Formulations of the invention are essentially non-irritating and non-allergenic. Compositions for use in delipidation should be essentially free of oil. The compositions of the invention are basically dry solids or aqueous solutions containing empty (uncomplexed) or loosely complexed cyclodextrin. For example,  $\alpha$ -,  $\beta$ - and  $\gamma$ -cyclodextrins, including substituted cyclodextrins may be used. The  $\beta$ - and  $\gamma$ - cyclodextrins appear to be particularly useful in the methods of the invention. The hydroxypropyl cyclodextrins are particularly useful either alone or in combination with other cyclodextrins. It is often useful to use more than one cyclodextrin so that there are different "holes" for purposes of complexing different substances in the ear canal or on the skin.

The use of cyclodextrins on a support provides a useful

means of application and treatment of patients who have conditions such as seborrhea or acne. The cyclodextrin is adsorbed or absorbed on or in the support. Supports may be, for example, a gauze, a sponge, cellulose such a paper, or 5 polymeric sheets and fabrics. The supports with the cyclodextrin may be placed in air-tight packaging such as foil or plastic sheets which are sealed. For emergency facilities they may be provided in containers of multiple pre-moistened supports. The cyclodextrin compositions may also be placed in 10 containers with dispensing means such as roll-on means, brushes, sponges, or fabrics which may placed at the container opening or be attached to the cap for easy application to affected areas. The administration of cyclodextrins using 15 moistened supports allows targeted delivery of the cyclodextrin-containing solution. Premoistened sheets provide a preferred method for continued exposure of the tissue to the cyclodextrin solution. Compositions for use in the method of the invention can also be applied as aerosols to be sprayed on the target area or sprayed on supports for application to the 20 target area. Other methods of application include roll-on, application by hand or brush or other means. Another method of application is by immersion in or sprinkling by water containing the cyclodextrin. Suitable carriers may be in the form of powder, oil-free gels or suspensions. However, the 25 carrier must not contain any component that complexes with the cyclodextrin in such a manner that it is not readily replaced by components to be removed from the skin or ear canal.

Aqueous compositions are a preferred class of compositions. However, the compositions may contain alcohols or other 30 carriers that are not firmly complexed to the cyclodextrin. The primary requirement of any composition of the invention is that the cyclodextrin either be empty of guest molecules or, if some component of the composition can be complexed, the guest molecules must be preferentially and easily displaced by 35 lipids or lipid-like materials.

Compositions for use in the ear canal may also be provided in the form of gels, lotions, and creams. However, it is

crucial that the composition contain no complexed molecules that are not easily displaced by components of cerumen, which is a mixture of debris, hair, dirt, and various lipid-like substances which include fatty acids and waxes. The components differ among patients.

For use in the ear canal, cyclodextrins in aqueous carriers present advantages of economy and ease of use. Cyclodextrin solutions containing between 1 and 30% by weight are preferred. A preferred concentration is about 10%. For use on the skin, the compositions may be in the form of powders or of liquid formulations. It is important that no components of the composition bind to the cyclodextrin which might fill the cyclodextrin cavity or render the cavity unaccessible, i.e., no additive should interfere with the complexing of lipids by the cyclodextrins. Because cerumen is a heterogeneous mixture of lipid-like substances, mixtures of cyclodextrins having different cavity sizes may be advantageously used in compositions for cleansing of the ear canal.

Compositions may also be used to delipidate hair and the scalp. Such compositions may be in the form of aqueous solutions for use as rinses or shampoos.

Example 1: Dissolution of skin lipids.

Sebum and other skin lipids were collected from facial skin by gentle scraping with a spatula. Small amounts of the lipid were applied to glass slides as thin smears, approximately 50  $\mu\text{g}/20 \text{ mm}^2$ . One slide (a) was covered with a water layer and the other slide (b) was covered with a 5% solution of hydroxypropyl- $\beta$ -cyclodextrin in water. The slides were shaken gently periodically at room temperature, and were then examined by transmitted light. No obvious changes were observed on the lipid smear of slide (a) over 30 minutes time. On slide (b), evidence of dissipation of lipids was seen in a few minutes. After 30 minutes, most of the lipid on slide (b) was gone, and the aqueous phase remained clear.

Example 2: Dissolution of cerumen:

The procedure of Example 1 was followed using cerumen collected from the ear. The results were similar to those

obtained with sebum.

Example 3: Absorption of lipids:

Glass slides containing thin smears of skin lipids were prepared as in example 1. Slide (a) was an untreated control. Powdered  $\beta$ -cyclodextrin was placed over the lipid layer of slide (b) and gently pressed down with a flat spatula without triturating or mixing. After 5 minutes at room temperature, both sides were gently rinsed several times with distilled water. Both were covered with water and examined by transmitted light. Slide (a) appeared to be substantially unchanged, and the film strongly repelled water. Only a trace of film remained on slide (b), and water was not repelled from the area where the smear had been applied.

Example 4: Skin test:

A female applied a very thin layer of  $\beta$ -cyclodextrin in water suspension to one side of the face and nose. The suspension applied smoothly and easily and gave a sensation of coolness. For a period of 4-6 hours thereafter, the treated skin appeared oil-free and lacked the shiny, moist, oily appearance of the untreated area.

Example 5: Skin test:

A male applied a very thin layer of powdered beta-cyclodextrin to one side of the face and nose, using his finger as an applicator. The powder applied smoothly and easily. The white powder was no longer visible after several minutes. The subject male remained in a warm room for two hours. Areas wherein the cyclodextrin had been applied appeared oil-free. Untreated areas had a shiny appearance and a moist, oily texture.

The test was repeated with powdered hydroxypropyl- $\beta$ -cyclodextrin. Similar results were obtained. The test using hydroxypropyl- $\beta$ -cyclodextrin was repeated. However, water was sprayed on the face after several minutes. Water on the untreated side formed droplets, indicating presence of lipids on the skin. Droplet formation was far less on the side which had been treated with cyclodextrin.

Example 6: Cerumen complexation:

Multiple samples of cerumen were prepared in the following manner: Ear wax from several patients was collected and combined with water by ultrasonication. The resulting suspension was coarsely filtered to remove hair and large particles. Aliquots of the suspension were then spotted onto polyethylene sheets and dried with warm air to form a yellowish waxy cerumen layer. The polyethylene sheets were cut into disks, each containing about 7 milligrams of cerumen.

10 Disks were placed in tubes containing different formulations:

#1: 10% weight aqueous solution of  $\gamma$ -cyclodextrin.

#2: Debrox from Marion Merrell Dow, Cincinnati, Ohio, containing urea peroxide, glycols and water.

15 #3: Cerumenex from Purdue Frederick, Norwalk, Connecticut, containing peptide oleate condensate and propylene glycol.

Results after 10 minutes:

20 #1: cerumen began to separate from the plastic disk, color was lightened, and cerumen/dextran complex had accumulated at the bottom of the tube. Upon swirling, the cerumen completely separated from the polyethylene disk and disintegrated.

#2 Small bubbles formed. Cerumen retained yellowish color and remained affixed to the polyethylene disks even after swirling.

25 #3 No bubbles. Cerumen retained yellowish color and remained affixed to the polyethylene disks even after swirling.

Example 7: Cerumen removal in human patients:

30 Compositions of Example 6 were tested in two human subjects. In each instance, the solution was warmed to body temperature and the ear canal filled with 20-30 drops of the solution. After 10 minutes, the solution was drained from the ear canal into a clear cup. The canal was then examined by otoscope.

35 In subject #1, Compositions #1 and #2 were tested by treating one ear with composition #1 and the other with composition #2.

Results:

Patient #1

Composition #1: Substantial reduction in cerumen was noted.

Recovered solution was cloudy and contained visible particles. No irritation was reported.

Composition #2: Little change in amount of cerumen in the ear. Solution recovered was substantially clear. No irritation was reported.

5

Patient #II

Composition # 1: Result was same as in patient #I.

10

Compositions #3: Result essentially the same as in patient #I when treated with composition #2, except that some irritation was reported several hours later.

Example 8: Cerumen removal in an AIDS patient:

Solution # 1 containing 10%  $\gamma$ -cyclodextrin in water was applied to ears by the method of Example 7. Ears were substantially cleared of wax. No irritation was reported.

15

The methods of the invention are particularly useful in immune compromised patients or patients with easily injured skin such as the elderly or children, since no mechanically abrasive method is required in practice of the invention.

20

The compositions for use in removing cerumen may advantageously be sold in bottles having tops equipped with droppers for administration into the ear canal. It is also possible to provide the droppers with the bottles or to provide kits for administration of the cyclodextrin-containing material for cleaning the ears using droppers and ear syringes for further cleaning of the ear.

25

Compositions for use in delipidation of the skin may be supplied on saturated sponges or other absorbent materials in sealed packages or may be provided in bottles with or without supports on which to adsorb the materials for application to the skin.

30

**CLAIMS:**

1. A composition for removal of cerumen from the ear canal comprising essentially empty cyclodextrin in a pharmaceutically acceptable carrier.
- 5 2. A composition of claim 1 wherein the cyclodextrin is present in a substantially oil-free solution at between about 1% and 30% by weight.
- 10 3. A composition of claim 1 wherein the cyclodextrin-containing composition consists essentially of cyclodextrin in water.
- 15 4. A composition of claim 3 wherein the cyclodextrins are selected from the group consisting of  $\alpha$ -cyclodextrins,  $\beta$ -cyclodextrins and  $\gamma$ -cyclodextrins.
5. A composition of claim 3 containing cyclodextrins having at least two different cavity sizes.
- 20 6. A skin and hair cleaning composition comprising cyclodextrins in an essentially oil-free carrier.
7. A composition of claim 6 in an aqueous carrier.
- 25 8. A composition of claim 6 which is a powder.
9. A composition of claim 6 wherein the cyclodextrin is present in a substantially oil-free solution at between about 1% and 30% by weight.
- 30 10. A composition of claim 6 wherein the cyclodextrin-containing composition consists essentially of cyclodextrin in water.

11. A composition of claim 9 wherein the cyclodextrins are selected from the group consisting of  $\alpha$ -cyclodextrins,  $\beta$ -cyclodextrins and  $\gamma$ -cyclodextrins.
- 5 12. A composition of claim 9 wherein containing cyclodextrins of at least two different cavity sizes.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/00401

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A01N 43/04; A61K 31/715, 9/50, 7,035, 7/06; C08B 37/16  
 US CL : 514/58; 536/103; 424/69, 70, 499

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/58; 536/103; 424/69, 70, 499

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4715369 (SUZUKI et al.) 29 December 1987, see column 4 lines 28-59 and claims 1-3.	1-12
X	US, A, 4,267,166 (YAJIMA) 12 May 1981, see column 1 lines 39-45, column 2 lines 59-60, and column 4 lines 13-21.	1-12
X	Wacker-Chemie GmbH Bulletin, June 1990, "Cyclodextrins and Derivatives: Gamma W8", see the whole bulletin.	1-4, 6-11

Further documents are listed in the continuation of Box C.

See patent family annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP, A, 01-193209 (SANRAKU OCEAN Co Ltd) 03 August 1989, see the Derwent abstract.	1-4, 6-11
X	JP, A, 03-287512 (SHISEIDO Co Ltd) 18 December 1991, see the Derwent abstract.	1-4, 6-11
X	FR, A, 2,640,136 (TSOMI) 15 June 1990, see the Derwent abstract.	1-4, 6-11

# INTERNATIONAL SEARCH REPORT

Int. dional application No.

PCT/US94/00401

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS—search terms: ?cyclodextrin, cyclodextrin?, cerumen, wax, skin, hair, wash?, clean?, delipidat?  
STN (files CA, EMBASE, MEDLINE, and WPIDS)—search terms: cyclodextrin#, cerumen, wax##, skin, hair, oil, clean?, remov?, ear, shampoo?, delipid?,